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EXAMINER	
RAWLINGS, STEPHEN L	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 08/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/684,890	ZENTGRAF ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 April 2004 and 10 October 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-26 and 29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-26 and 29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The amendment filed October 10, 2002 is acknowledged and has been entered. Claims 27 and 28 have been canceled. Claims 13, 17-19, 21, and 23-26 have been amended. Claim 29 has been added.

2. The amendment filed February 6, 2003 is acknowledged and has been entered. Claims 13, 23, and 24 have been amended.

3. The amendment filed October 14, 2003 is acknowledged and has been placed in the record, but not entered for the reason set forth in the Office communication mailed March 10, 2004.

4. The amendment filed April 9, 2004 is acknowledged and has been entered. Claims 13, 23, and 24 have been amended.

5. Claims 12-26 and 29 are pending in the application and are currently subject to prosecution.

Grounds of Objection and Rejection Withdrawn

6. Unless specifically reiterated below, Applicant's amendment, in view of Applicant's arguments, have obviated the grounds of objection and rejection set forth in the Office action mailed July 10, 2002.

Response to Amendment

7. The amendment filed October 10, 2002 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material, which is not supported by the original disclosure, is the

amino acid sequence of accession number Y08612 and the nucleic acid sequence encoding the protein of accession number Y08612 at page 6.

Applicant is required to cancel the new matter in the reply to this Office Action; or alternatively, as the added material is material incorporated by reference to a non-patent publication, Applicant must provide an affidavit or declaration executed by Applicant, or a practitioner representing Applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

Specification

8. The specification is objected to because the use of numerous improperly demarcated trademarks has been noted in this application. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

An example of an improperly demarcated trademark is GenBank™ (page 4, line 4).

Appropriate correction is required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate symbol indicating its proprietary nature (e.g., ™, ®), and accompanied by generic terminology. Applicants may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the Internet at http://www.uspto.gov/web/menu/search.html.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to

> enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 13-26 and 29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a new matter rejection.

Claims 13, 23, and 24 recite SEQ ID NO: 2. At page 5 of the amendment filed October 10, 2002, Applicant has cited MPEP § 2406.01 and implied that the incorporation of the amino acid sequence set forth as GenBank™ accession number Y08612 introduces no new matter, since the specification, as originally filed, refers to said accession number at page 4, line 4. MPEP § 608.01(p) does not provide for the incorporation by reference of essential material by reference to non-patent publications. "Essential material" is defined as "that which is necessary to (1) describe the claimed invention, (2) provide an enabling disclosure of the claimed invention, or (3) describe the best mode (35 U.S.C. 112)". The amino acid sequence set forth as GenBank™ accession number Y08612 is essential information because the disclosure of said amino acid sequence is necessary to both describe and enable the claimed invention, since the claims are drawn, for example, to a method comprising determining the amount of a protein having the amino acid sequence. Applicant has thus necessarily amended the specification and the claims to include the material incorporated by reference to GenBank™ accession number Y08612. However, such an amendment must be accompanied by an affidavit or declaration executed by Applicant, or a practitioner representing Applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. Otherwise, and until such a time that said affidavit or declaration has been provided, because the nucleic acid sequence and the amino acid sequence identified by the accession number is subject to change,

the recitation of the amino acid sequence set forth as SEQ ID NO: 2 in the claims is deemed to introduce new matter. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

11. Claims 13-26 and 29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a new matter rejection.

Claim 13 recites "non-cancer cells". As amended by the amendment filed October 10, 2002, it appears that Applicant has not pointed to any particular disclosure in the specification, including the claims, as originally filed, which Applicant believes provide the necessary written support for the claim language. MPEP § 2163 states, "when filing an amendment an applicant should show support in the original disclosure for new or amended claims". See MPEP § 714.02 and § 2163.06. Nevertheless, as MPEP § 2163 further states: The examiner has the initial burden of presenting evidence or reasoning to explain why persons skilled in the art would not recognize in the original disclosure a description of the invention defined by the claims. See Wertheim, 541 F.2d at 263, 191 USPQ at 97". While the specification discloses "normal mucosa", "normal lymphocytes", and "normal (control) adult female breast" in the context of particular examples in which comparisons of the expression levels of the protein in these normal cells and tumor cells of the same tissue type were made, the specification does not describe the genus of "non-cancer cells" and therefore it appears the specification fails to provide proper and sufficient written support for the recitation of "non-cancer cells" in the instant claims. Accordingly, the recitation of "non-cancer cells" appears to introduce new matter and thereby

violates the written description requirement set forth under 35 USC § 112, first paragraph.

Claim 18 recites "annealing" and "specifically"; and claim 24 recites "anneals specifically". As amended by the amendment filed April 18, 2002, it appears that Applicant has not pointed to any particular disclosure in the specification, including the claims, as originally filed, which Applicant believes provide the necessary written support for "annealing" or "anneals". At page 6, lines 4 and 5, the specification discloses "the use of nucleic acid binding molecules binding to the transcript of Nup88", but the specification does not appear to provide proper and sufficient written support for "annealing". While a nucleic acid molecule might bind another nucleic acid molecule by annealing, it may not, since it might bind by intercalation, as would a triplex-forming oligonucleotide, for example.

In addition, regarding the recitation of "specifically" in the claims 18 and 24, as amended by the amendment filed October 10, 2002, again it appears that Applicant has not pointed to any particular disclosure in the specification, including the claims, as originally filed, which Applicant believes provide the necessary written support for "specifically". While the nucleic acid binding molecule, if it were a nucleic acid molecule, might bind specifically, it may also bind non-specifically, or non-exclusively, depending upon the definition of the term "specificity" that might be applied. The disclosure at page 6 of the specification does not provide proper and sufficient written support for the recitation of "specifically" in the context of claims 18 and 24.

It therefore appears that the recitation of "annealing" or "anneals" and "specifically" in claims 18 and 24 introduces new matter and thereby violates the written description requirement set forth under 35 USC § 112, first paragraph.

Claims 25 and 26 recite "in part". As amended by the amendment filed April 18, 2002, it appears that Applicant has not pointed to any particular disclosure in the specification, including the claims, as originally filed, which Applicant believes provide the necessary written support for "in part". At page 6,

line 15, the specification discloses the kit can comprise "an antigenic part" of the protein Nup88. However, the specification does not appear to provide proper and sufficient written support for "in part", since it appears that only an antigenic part, not any part, of the protein has been contemplated as a component of the kit.

These issue might be resolved if Applicant were to point to particular disclosures in the specification, including the claims, as originally filed, which Applicant believes provide the necessary written support for present claim language.

12. Claims 18, 23, 25, and 29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a written description rejection.

Claim 23 is drawn to a kit comprising "a protein binding molecule", which binds to the protein consisting of the amino acid sequence set forth as SEQ ID NO: 2. The claim therefore encompasses a kit comprising a member of a broad genus of substances that bind the protein of SEQ ID NO: 2, including but not limited to such structurally and functionally unrelated molecules as an antibody, a protease, a cofactor, and a ligand. However, the specification merely describes an antibody that binds the protein without describing the particular structures of any other substance that binds the protein, e.g., a cofactor. Moreover, the mere disclosure of an antibody that binds the protein cannot be regarded as representative of the genus of protein binding molecules to which the claims are directed, because Applicant's have not disclosed any particularly identifying feature that is common to at least a substantial number of the members of the genus and exemplified by the antibody. Accordingly, the disclosure would not

reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed because the skilled artisan could not instantly envision, recognize, or distinguish at least a substantial number of the members of the genus of protein binding molecules to which the claims are directed.

Claim 18 is drawn to a method comprising the use "a nucleic acid binding molecule". The nucleic acid binding molecule is not necessarily a nucleic acid. The claim therefore encompasses a method comprising the use of a member of a broad genus of substances that "anneal" to a transcript encoding the protein of SEQ ID NO: 2, including but not limited to such structurally and functionally unrelated molecules as a complementary oligonucleotide, a ribozyme, a triplex-forming oligonucleotide, and a protein-nucleic acid (PNA) molecule. However, the specification merely describes a nucleic acid molecule encoding the protein and its complement, and perhaps portions thereof. Accordingly, the disclosure would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed because the skilled artisan could not instantly envision, recognize, or distinguish at least a substantial number of the members of the genus of nucleic acid binding molecules to which the claims are directed.

MPEP § 2163.02 states, "[a]n objective standard for determining compliance with the written description requirement is, 'does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed' ". The courts have decided:

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.*

See *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Federal Circuit, 1991). Furthermore, the written description provision of 35 USC § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention

and reference to a potential method for isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016.

The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, ``Written Description" Requirement (66 FR 1099-1111, January 5, 2001) state, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). The *Guidelines* further state, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species *cannot* be achieved by disclosing only one species within the genus" (Id. at 1106); accordingly, it follows that an adequate written description of a genus cannot be achieved in the absence of a disclosure of at least one species within the genus. Because the claims encompass a genus of variant species, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. However, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; nor has Applicant shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; nor has Applicant described distinguishing identifying characteristics sufficient to show that Applicant had possession of the claimed invention at the time the application was filed.

Furthermore, in deciding *The Reagents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the Court held that a generic statement that defines a genus of nucleic acids *by only their functional activity* does not provide

an adequate written description of the genus. By analogy, a generic statement that defines a genus of protein binding molecules by only their common ability to bind the polypeptide of SEQ ID NO: 2 does not serve to adequately describe the genus as whole. The Court indicated that while applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a precise definition of a representative number of members of the genus, such as by reciting the structure, formula, chemical name, or physical properties of those members, rather than by merely reciting a wish for, or even a plan for obtaining a genus of molecules having a particular functional property. The recitation of a functional property alone, which must be shared by the members of the genus, is merely descriptive of what the members of genus must be capable of doing, not of the substance and structure of the members.

Finally, regarding claim 29, which is drawn to the method of claim 17, wherein the antibody is a "natural antibody", the specification describes monoclonal antibodies. The breadth of a claim directed to a genus of natural antibodies, which bind the polypeptide of SEQ ID NO: 2, is not equal to a claim directed to a genus of monoclonal antibodies having that binding specificity. For example, a natural antibody can be a human antibody, which may not be considered a monoclonal antibody, since the latter is typically produced by a hybridoma. Moreover, the specification does not describe a naturally occurring human antibody, only a non-naturally occurring monoclonal antibody produced by a hybridoma cell line. Accordingly, Applicant's disclosure would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time application was filed.

13. Claims 13-22 and 29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using a method for identifying the presence of a malignant tumor in a tissue biopsy sample comprising determining the amount of the polypeptide of SEQ ID NO: 2 using an antibody

that binds the polypeptide of SEQ ID NO: 2, wherein said antibody is a monoclonal antibody, a polyclonal antibody or a recombinant or chimeric molecule comprising each of the six CDRs of the monoclonal antibody bearing the accession number DSM ACC 2457, or comprising determining the amount of a transcript encoding said polypeptide using an oligonucleotide that binds the transcript encoding said polypeptide, whereby the presence of malignant tumor is identified if said amount is greater than the amount in normal control tissue, does not reasonably provide enablement for using a method for identifying the presence of a benign tumor in a tissue biopsy sample, or for using a method for identifying the presence of a malignant tumor in a tissue biopsy sample comprising determining the amount of the polypeptide of SEQ ID NO: 2 using an antibody that binds the polypeptide of SEQ ID NO: 2, wherein said antibody is an antibody comprising fewer than the six CDRs of the monoclonal antibody bearing the accession number DSM ACC 2457. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The amount of guidance, direction, and exemplification set forth in Applicant's disclosure would not be sufficient to enable the skilled artisan to use the claimed invention without a need to first perform an undue amount of additional experimentation. Factors to be considered in determining whether undue experimentation is required are summarized in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986). These factors include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are drawn to a method for identifying a cancer cell comprising determining if a tissue biopsy sample comprises cells that express more of the

protein consisting of the amino acid sequence set forth as SEQ ID NO: 2, or more of a transcript encoding said protein, than non-cancer cells. At pages 2, line 27, through page 3, line 18, the specification describes the "cancer cells" that might be identified using the claimed invention. The list of "cancer cells" notably includes "protruberous giant cell tumor (benign)" (page 3, lines 15) and "benign mesothelioma" (page 3, line 18). However, at page 22, the specification discloses the invention cannot be used to identify benign giant cell tumor cells and cannot be used to identify benign mesothelioma cells. Having examined the expression of the polypeptide of SEQ ID NO: 2, i.e., Nup88, in a variety of different tumor specimens, Gould et al. (*Am. J. Pathol.* **157**: 1605-1613, 2000) similarly teaches, "samples from two benign cystic mesotheliomas (multiple peritoneal inclusion cysts) were consistently negative" (page 1609, column 2). Gould et al. also discloses that benign giant cell tumor cells do not express the protein; see page 1607, Table 1. Gould et al. concludes, "Nup88 was either sporadic or not detectable in most benign tumors and hyperplasias" (page 1611, column 2). Accordingly, it appears that the skilled artisan cannot predict whether the claimed invention can be used to identify the presence of benign tumor cells in a biopsy sample and moreover could not use the claimed invention without having to first perform an undue amount of additional experimentation to determine if the invention can be used to identity non-malignant tumor cells in biopsy samples.

In addition, the amount of the amount of guidance, direction, and exemplification set forth in Applicant's disclosure would only be sufficient to enable the skilled artisan to make an antibody that binds the polypeptide of SEQ ID NO: 2 or an oligonucleotide that binds the transcript encoding said polypeptide without having to first perform an undue amount of additional experimentation. Moreover, the disclosure would not enable the skilled artisan to make any of other molecules that bind the polypeptide of SEQ ID NO: 2, including, for example, cofactors and ligands, in addition to non-specific binding molecules, e.g., a protease. One cannot make what has not been described without a need

to perform an undue amount of additional experimentation; and Applicant's have not described cofactors and ligands that bind the polypeptide of SEQ ID NO: 2, which according to the disclosure might be used to practice the claimed invention.

Furthermore, the amount of guidance, direction, and exemplification provided by Applicant's disclosure would only be sufficient to enable the skilled artisan to make an antibody that is a chimeric molecule that comprises each of the six CDRs of the monoclonal antibody bearing the accession number DSM ACC 2457. Mariuzza et al (*Annu. Rev. Biophys. Biophys. Chem.* **16**: 139-159, 1987) reviews the structural basis of antigen-antibody recognition and thus defines the state of the art. A naturally occurring antibody comprises two polypeptides, the so-called light and heavy chains. The antigen-combining site of an antibody is a three-dimensional structure, which fully comprises six "complementarity-determining regions" (CDRs), three each from the light and heavy chains. The amino acid sequences of the CDRs are hypervariable, as the amino acid residues contained within the CDRs determine much of antibody's antigen-binding specificity. Of the amino acid residues of the antibody contacting the antigen, six are within the light chain, nine are within the heavy chain, and two are within the constant or nearly constant "framework" regions. As the claims encompass a grafted antibody that comprises fewer than three light chain CDRs and/or fewer than three heavy chain CDRs, while the artisan would not expect such an antibody to bind specifically to an antigen, the specification fails to teach one to make such an antibody, which retains specific binding affinity for the polypeptide of SEQ ID NO: 2. Thus, the amount of guidance, direction, and exemplification set forth by Applicant is not reasonably commensurate in scope with the claims and would not be sufficient to enable the skilled artisan to make the claimed invention without the need to perform an undue amount of additional experimentation.

As evidenced by the teachings of the references cited above to address the level of skill in the art and the state of the art, now and as of the earliest filing

date sought by Applicant in the instant application, the art is characterized by a high level of complexity, as well as unpredictability. Upon considering the nature of the invention and the breadth of the claims, it appears that the amount of guidance, direction, and exemplification set forth by Applicant is not reasonably commensurate in scope with the claims. Therefore, although the relative skill of those in the art is high, absent a sufficient disclosure to enable the use of the claimed invention, an undue amount of additional experimentation, that is, beyond the realm of routine experimentation, would have to be performed before the claimed invention, commensurate in scope with the claims, could be made and used.

In conclusion, upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with *Ex parte Forman*, 230 USPQ 546 (BPAI 1986), the amount of guidance, direction, and exemplification disclosed by Applicant is not deemed sufficient to enable the skilled artisan to use the claimed invention without a need to perform an undue amount of additional experimentation.

14. Claims 23-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making and using a diagnostic kit for diagnosing a malignant tumor comprising an antibody that binds the polypeptide of SEQ ID NO: 2 or an oligonucleotide that binds the transcript encoding said polypeptide, wherein said antibody is a monoclonal or polyclonal antibody, or a recombinant or chimeric molecule comprising each of the six CDRs of the monoclonal antibody bearing the accession number DSM ACC 2457, does not reasonably provide enablement for making and using a diagnostic kit for diagnosing any tumor, including a benign tumor, comprising any antibody that binds the polypeptide of SEQ ID NO: 2 or any oligonucleotide that binds the transcript encoding said polypeptide, wherein said antibody is comprises fewer than the six CDRs of the monoclonal antibody bearing the accession number DSM ACC 2457. The specification does not enable any person skilled in the art

to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

For the reasons set forth above, to the extent that the claims are drawn to a kit for diagnosing cancer, the amount of guidance, direction, and exemplification set forth in Applicant's disclosure would not be sufficient to enable the skilled artisan to use the claimed invention without a need to first perform an undue amount of additional experimentation. In addition, as the claims are not limited to a kit for diagnosing cancer, it is duly noted that apart from malignant tumors, the amount of guidance, direction, and exemplification set forth in Applicant's disclosure would not be sufficient to enable the skilled artisan to use the claimed invention to diagnose any other disease without a need to first perform an undue amount of additional experimentation. Moreover, there is no objective evidence that the expression level of the polypeptide of SEQ ID NO: 2 is associated with disease other than a cancerous malignancy.

Regarding the sufficiency of the disclosure to enable the skilled artisan to make the claimed invention, the amount of the amount of guidance, direction, and exemplification set forth in Applicant's disclosure would only be sufficient to enable the skilled artisan to make a kit comprising an antibody that binds the polypeptide of SEQ ID NO: 2 or an oligonucleotide that binds the transcript encoding said polypeptide without having to first perform an undue amount of additional experimentation. Claims 23 and 25 encompass a kit comprising a broad genus of molecules that bind the polypeptide of SEQ ID NO: 2, including, for example, cofactors and ligands, in addition to non-specific binding molecules, e.g., a protease. Thus, the amount of guidance, direction, and exemplification set forth in Applicant's disclosure is not reasonably commensurate in scope with the claims; and one cannot make what has not been described without a need to perform an undue amount of additional experimentation.

Finally, to the extent that claims 23 and 25 are drawn to a kit comprising an antibody, which is a chimeric molecule, for the reasons set forth above, the amount of guidance, direction, and exemplification provided by Applicant's

disclosure would only be sufficient to enable the skilled artisan to make such a chimeric molecule that comprises each of the six CDRs of the monoclonal antibody bearing the accession number DSM ACC 2457.

In conclusion, upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with *Ex parte Forman*, 230 USPQ 546 (BPAI 1986), the amount of guidance, direction, and exemplification disclosed by Applicant is not deemed sufficient to enable the skilled artisan to make and use the claimed invention without a need to perform an undue amount of additional experimentation.

15. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

16. Claims 13-22 and 29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 13-22 and 29 are indefinite because claim 13 does not recite a positive correlation step that clearly relates the method steps recited in the body of the claim to the preamble of the claim. As written, claim 13 recites the phrase "wherein a sample comprising said protein at a level of expression that is greater than non-cancer cells indicates that said sample comprises a cancer cell" in the last line. However, this phrase is not considered a positive correlation step, because the preamble of claim 13 recites, "for identifying a cancer cell". It cannot be ascertained how determining if a sample comprises a cancer cell identifies a cancer cell. It may be said that determining if a sample comprises a cancer cell identifies the presence of a cancer cell, but claim 13 does not recite an active step in which a cancer cell is identified as, for example, a particular type of cancer cell. For this reason, the metes and bounds of the claimed invention are not sufficiently delineated to satisfy the requirements set forth under 35 USC § 112, second paragraph.

Claim Rejections - 35 USC § 102

17. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

18. Claims 13, 15-17 and 29 are rejected under 35 U.S.C. 102(a) as being anticipated by Martinez et al. (*Cancer Res.* **59**: 5408-5411, 1999) (of record).

Claims 13, 15-17 and 29 are drawn to a method for identifying a cancer cell comprising providing a tissue biopsy sample from a human and determining the level of expression of the polypeptide of SEQ ID NO: 2 by a process comprising binding a natural antibody to said polypeptide.

Martinez et al. teaches analyzing tissue biopsy samples to determine if the polypeptide of SEQ ID NO: 2, i.e., Nup88, is overexpressed in malignant ovarian tissue, as compared to healthy adjacent tissue; see entire document (e.g., the abstract). Martinez et al. teaches a polyclonal antibody that binds Nup88 (page 5408, column 1), which can be used to make the determination by immunohistochemical methods; see, e.g., page 5410, column 1.

19. Claim 24 is rejected under 35 U.S.C. 102(b) as being anticipated by Boehringer Mannheim *Biochemicals,* 1994 Catalog (No. 1034 731/1006 924), page 93, which is of record, for essentially the same reason as that set forth at page 16 (section 14) of the Office action mailed July 10, 2002.

Claim 24 is drawn to a kit comprising a nucleic acid molecule that anneals specifically to a nucleic acid transcript that encodes the protein of SEQ ID NO: 2. Although claim 24 recites the kit is "diagnostic", this recitation is viewed as a recitation of intended use only.

Boehringer Mannheim teaches a kit comprising random primers of all possible 6-nucleotide sequences. The kit therefore comprises a nucleic acid molecule that will anneal specifically to a transcript encoding the polypeptide of SEQ ID NO: 2, since the kit comprises a primer having a polynucleotide sequence that is completely complementary to any six contiguous nucleotides of the polynucleotide sequence of the transcript.

At page 14 of the amendment filed October 10, 2002, Applicant has traversed the previously stated ground of rejection arguing that the random primers do not specifically bind the transcript and that the term "specifically" in the context of the claim would be understood to mean that the claimed invention must comprise a nucleic acid molecule that binds exclusively to the transcript.

Applicant's argument has been carefully considered but not found persuasive for the following reasons:

The artisan would appreciate that a nucleic acid molecule comprising a polynucleotide sequence that is fully complementary to the transcript anneals (i.e., binds) specifically, albeit not necessarily exclusively to the transcript. Accordingly, the random primers of which the kit of the prior art is comprised, which have a six nucleotide sequence that is fully complementary to any six contiguous nucleotides of the polynucleotide sequence of the transcript, will bind specifically to the transcript.

Claim Rejections - 35 USC § 103

20. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

21. Claims 13, 14, and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Martinez et al. (*Cancer Res.* **59**: 5408-5411, 1999) (of record).

Claims 13, 14, and 18 are drawn to a method for identifying an epithelial tumor cell comprising providing a tissue biopsy sample and determining the level of expression of the polypeptide of SEQ ID NO: 2 by annealing a nucleic acid molecule that specifically binds a transcript encoding said polypeptide to said transcript.

Martinez et al. teaches that which is set forth above, but does not expressly teach identifying a cancer cell in a tissue biopsy sample by determining the level of expression of the polypeptide of SEQ ID NO: 2 by a method that comprises annealing a nucleic acid that binds the transcript encoding the protein.

In addition, although most ovarian tumors are of epithelial cell origin, Martinez et al. does not expressly teach identifying an epithelial tumor cell.

Nevertheless, Martinez et al. teaches analyzing multiple epithelial tumor cell lines (i.e., ovarian adenocarcinoma cell line SK-OV-3, ovarian cystoadenocarcinoma cell line OAW42, cervical adenocarcinoma cell line HeLa, cervical squamous cell carcinoma cell line SiHa, breast adenomcarcinoma cell line MCF7, and breast carcinoma cell line BT-20) to determine if the polypeptide of SEQ ID NO: 2, i.e., Nup88, is overexpressed, as compared to non-transformed cell lines; see entire document (e.g., the abstract). Martinez et al. teaches a nucleic acid molecule that binds the transcript encoding the protein (page 5408, column 1), which can be used to make the determination by Northern blot analysis; see, e.g., page 5409, Figure 2. Martinez et al. teaches Nup88 is strongly expressed in a series of human tumor cell lines compared with non-transformed cell lines at the RNA and protein levels (abstract). Moreover, Martinez et al. discloses, "the level of Nup88 mRNA expression in the tumor cell lines was always higher than in the normal cells" (page 5410, column 1).

Accordingly, it would have been *prima facie* obvious to one of ordinary skill in the art at the invention was made to identify a cancer cell, or more particularly an epithelial cancer cell, in a tissue biopsy sample by determining if the

polypeptide of SEQ ID NO: 2, i.e., Nup88, is overexpressed, as compared to non-transformed cell lines, using a Northern blot assay comprising annealing a nucleic acid molecule that binds the transcript encoding the protein. One ordinarily skilled in the art at the time of the invention would have been motivated to do so to identify the presence of cancer cells, or more particularly epithelial cancer cells in a tissue biopsy sample.

22. Claims 13, 17, 19, 21, and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Martinez et al. (*Cancer Res.* **59**: 5408-5411, 1999) (of record) in view of US Patent No. 5,366,866 A.

Claims 13, 17, 19, 21, and 29 are drawn to a method for identifying a cancer cell comprising providing a tissue biopsy sample from a human and determining the level of expression of the polypeptide of SEQ ID NO: 2 by a process comprising binding a monoclonal antibody or a chimeric molecule to said polypeptide.

Martinez et al. teaches that which is set forth above, but does not teach or suggest the antibody that binds the polypeptide of SEQ ID NO: 2 be a monoclonal antibody or chimeric molecule.

US Patent No. 5,366,866 A ('866) teaches a method for detecting the presence of cancer cells, including epithelial cancer cells, and more particularly ovarian epithelial cancer cells, in a tissue biopsy, which employs an antibody that binds an antigen that is overexpressed by cancer cells, as compared to normal, non-cancer cells; see entire document (e.g., the abstract; column 5, lines 24-30; column 7, lines 7-12). '866 teaches the antibody that binds the antigen can be a polyclonal antibody, a monoclonal antibody, or chimeric molecule (column 7, lines 7-12).

It would have been *prima facie* obvious to one ordinarily skilled in the art at the time of the invention to have used either a monoclonal antibody or a chimeric molecule having the binding specificity of the polyclonal antibody of Martinez et al. to determine the expression level of the polypeptide of SEQ ID

NO: 2 in the tissue biopsy sample, because '866 teaches that either a polyclonal antibody, a monoclonal antibody, or chimeric molecule having the required binding specificity can be used to identify tissue biopsy samples comprising epithelial cancer cells, including ovarian cancer cells. One ordinarily skilled in the art at the time of the invention would have been motivated to do so to identify the presence of cancer cells, including in particular epithelial cancer cells, in a tissue biopsy sample.

23. Claims 23 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Martinez et al. (*Cancer Res.* **59**: 5408-5411, 1999) (of record) in view of US Patent No. 5,366,866 A.

Claims 23 and 25 are drawn a diagnostic kit comprising an antibody that binds the polypeptide of SEQ ID NO: 2 and further comprises, in whole or in part, said polypeptide.

Martinez et al. teaches that which is set forth above, but does not teach or suggest a diagnostic kit comprising the antibody that binds the polypeptide of SEQ ID NO: 2 and further comprising, in whole or in part, said polypeptide.

US Patent No. 5,366,866 A ('866) teaches that which is set forth above. In addition, '866 teaches diagnostic kits, which can comprise the antibody that binds the antigen and a control reagent, or more particularly the specific binding partner of the antibody, i.e., the antigen; see, e.g., column 6, lines 41-62.

It would have been *prima facie* obvious to one ordinarily skilled in the art at the time of the invention to make a diagnostic kit comprising a polyclonal antibody, a monoclonal antibody, or a chimeric molecule having the binding specificity of the polyclonal antibody of Martinez et al., which can be used diagnostically to identify the presence of a cancer cell by determining the expression level of the polypeptide of SEQ ID NO: 2 in the tissue biopsy sample, because '866 teaches that a kit comprising either a polyclonal antibody, a monoclonal antibody or chimeric molecule having the required binding specificity and the antigen to which the antibody specifically binds for use as a control

reagent can be used to identify tissue biopsy samples comprising epithelial cancer cells, including ovarian cancer cells. As kits are well known in the art to provide ease and convenience, one ordinarily skilled in the art at the time of the invention would have been motivated to do so to provide an easily accessible and convenient set of reagents for use in identifying the presence of cancer cells, including in particular epithelial cancer cells, in a tissue biopsy sample.

Conclusion

24. Having satisfied the deposit requirements, claim 12 has been allowed. Claims 13-26 and 29 are not allowed.

25. The art made of record and not relied upon is considered pertinent to Applicant's disclosure. Bastos et al. teaches antibodies that bind Nup88 and probes that bind a transcript encoding the protein. Matsuoka et al. teaches monoclonal antibodies that bind to nuclear pore proteins. Boer et al. teaches a protein that binds Nup88. Fornerod et al. (*EMBO J.*) teaches proteins and antibodies that bind Nup88 and probes the bind a transcript encoding the protein. Fornerod et al. (*Genomics.*) teaches probes the bind a transcript encoding the Nup88. US Patent Nos. 6,441,143 B1, 6,312,908 B1, and 6,682,901 B2 teaches diagnostic methods and kits.

26. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571) 272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

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